REMARKS

Reconsideration of this application is requested. Claims 1-11 and 15-22 are active in the application subsequent to entry of this amendment. Response is now provided to the issues raised in the outstanding Official Action in the order presented reference being made to the numbered paragraphs of the Action.

1. Applicants have evidence that a certified copy of the underlying Italian priority application was submitted to WIPO. Attached is a copy of WIPO form 304 stating that a certified copy of the priority document was received. In addition, as explained in more detail below, attached to this response is a verified English translation of the priority document thereby completing applicant's claim for benefit of priority under 35 U.S.C. § 119 (b).

2. Instructions are given to insert relevant section headings in the specification responsive to the examiner's suggestion.

With regard to claim 2 and the Deposit mentioned in that claim, applicant confirms that the microorganism claimed in claim 2 has been deposited under the Budapest Treaty as indicated in applicant's specification at page 3, lines 8-11. Attached is a Declaration signed by the attorney of record with regard to this Deposit thus resolving the issues raised in item 2 of the Official Action.

The claims have been amended in order to address the issues raised in item 4 of the Official Action. More specifically, claim 2 has been revised to adopt the terminology suggested by the examiner with one minor exception--the recitation "mutants or derivatives thereof" means any strain derived from the claimed one and being arginine-utilizing *Lactobacillus brevis*.

A typographical error does occur in claim 3, as the examiner noted, and the claim has been corrected accordingly. Basis for the appropriate ratio may be found in the specification at page 3, line 14.

Claim 6 has been amended as suggested.

As to claim 8, the applicant meant to distinguish a sucking tablet from a generic tablet, since sucking tablets are sucked, in order to release the active ingredient in a long period of time and provide for absorption by buccal mucosa. This is in contrast to a generic tablet, which can be swallowed whole, or chewed and then swallowed, the active ingredient is passed from mouth to gastroentestinal tract in a short time, and the absorption is generally different from the one occurring at buccal level. Further, since one possible embodiment of the present invention is directed to the treatment of the oral cavity (see claims 21 and 22), a sucking tablet is one of the most appropriate formulations for carrying out this embodiment. The difference shall be further appreciated by looking at Example 2 and Example 5.

Claims 15, 16 and 18 have been revised as suggested.

5-6. Claims 12-14 have been revised and written as appropriate method claims 19-22.

Claim 10 was amended in the Preliminary Amendment of December 21, 2001 and addresses the issues noted by the examiner.

Having resolved the formalities issues raised in the outstanding Official Action, attention is now directed to the art-based rejection.

9. Claims 1-18 are rejected as being either anticipated by or obvious over EP 0 956 858 cited in the International Search Report (of record in this application) as a category "P" document that is, not prior art but a publication falling between the priority date and the date of filing of the International application. The document referred to by the examiner was published on November 17, 1999.

The present application enjoys a priority date of June 21, 1999. The cited reference was published on November 11, 1999, after the invention by the applicant for a patent.

As noted above, WIPO did receive a certified copy of the underlying priority document and, according to standard practice, would have furnished a copy to the U.S. PTO. Further, applicant submits herewith an English translation of the priority document thereby completing his claim for benefit of priority under 35 U.S.C. 119. Accordingly,

applicant's claimed benefit of priority has been perfected and the claims of this application are entitled to a date prior to the date of publication of the document cited and relied upon. The document is therefore no longer competent as a prior art reference.

In any event, the herein claimed invention is patentably distinct over the cited EP 0 956 858 (hereinafter "EP") for the following reasons.

First the examiner will note that the *Lactobacillus casei* ATCC 8350 disclosed in the cited reference does not produce H_2O_2 (see Table 3).

Claim 1 requires at least one strain of H_2O_2-producing lactic acid bacteria. Therefore, the skilled person, in order to carry out the claimed invention, will select a H_2O_2-producing *Lactobacillus casei* discarding *Lactobacillus casei* theATCC 8530 of the cited reference, hence will look for a new *Lactobacillus casei*.

Also, in the case the skilled person would select a H_2O_2-producing lactic acid bacteria different from the new *Lactobacillus casei* according to the present invention, the skilled person might use the H_2O_2-producing lactic acid bacteria taught by the reference, i.e. the *Lactobacillus salivarius* or the *Lactobacillus gasseri*. But the skilled person, in order to make the claimed invention, must also select an arginine-utilizing lactic acid bacteria and this teaching is lacking in the cited reference, namely, the skilled person is unaware that of the possible lactic acid bacteria taught in EP, other than ones producing H_2O_2, are arginine-utilizing strains.

Therefore, by selecting a H_2O_2-producing lactic acid bacteria and an arginine-utilizing lactic acid bacteria, a new combination is provided.

The new technical effect provided by the new combination will be discussed in connection with the non-obviousness of the claimed subject matter. The claimed invention is not obvious over EP 0 956 858 (assuming *arguendo* it is competent prior art) because the claimed combination has an effect different than the combination of the art.

The claimed combination has, among others, the effect of inhibiting the growth of pathogenic agents; see Example 1. The combination of EP has the effect of inhibiting the adhesion of *Candida albicans* to HeLa cells. The effect of the claimed invention is directly on the pathogenic agent, so the pathogenic agent is stopped in its action. On the

contrary, EP shows a competitive action on the pathogenic agent, which is lessened in its infective action, but is not stopped in its growth.

Of the species of *lactobacilli* disclosed in EP, only *brevis, gasseri and fermentum* fall under group b) of claim 1. Even if those strains inherently are arginine-utilizing lactic acid bacteria, only *brevis* is essential to the invention of the reference (see claim 1 of the EP application).

The inventor's statement made on page 2, lines 3-6 of the application must be given considerable weight. It is important to notice in this statement that arginine-utilizing lactic acid bacteria were not known to have antibacterial or flora-regulating action in body orifices and on mucous membranes.

While EP is focused only on the treatment of vaginosis and vaginitis, see claim 1, the invention claimed herein broadly applies to the prevention and/or treatment of infections and inflammatory conditions caused by bacteria, viruses and fungi, especially in the mouth, vagina, urethra, nose, eyes and ears--note especially method claim 20.

The skilled person will immediately perceive the surprising and advantageous character of the claimed invention.

The skilled person knows that the mouth, vagina, urethra, nose, eyes and ears are very different districts of the body and each one has its own ecology as to the bacterial flora; EP relates only to bacterial specially selected for vaginal epithelium (see page 3, lines 13-15). Therefore, the skilled person would not have been encouraged by EP to test the lactic acid bacteria on other body orifices or mucous membranes.

Also of considerable importance, the skilled person, at the time the invention was made did not know from EP that, other than the two H_2O_2-producing *Lactobacillus salivarius* or the *Lactobacillus gasseri* (used in the present invention as arginine-utilizing strain), the other strains could have been arginine-utilizing. Moreover, the skilled person did not know that arginine-utilizing strains could have had a flora-regulating action in body orifices and on mucous membranes.

EP gives no suggestion of the growth-inhibiting activity of the claimed combination.

For arriving at the claimed invention, the additional teaching of WO 99/42568, the secondary reference, is useless to the skilled person. In fact, the cited reference discloses the pro-apoptotic activity of the arginine-utilizing lactic acid bacteria, but does not suggest that these strains, once combined with H_2O_2-producing lactic acid bacteria, would have enhanced the anti-infective activity of the latter strains. This synergistic effect is totally surprising, since arginine-utilizing strains are practically devoid of any activity in inhibiting the growth of pathogenic agents (see Example 1, in particular pages 7-9).

Accordingly, the claimed invention enriches the art with a new combination having a totally unexpected effect, and this fact should be recognized by the allowance of the claims on record.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached pages are captioned "**Version With Markings To Show Changes Made.**"

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION

Page 1, paragraph beginning on line 12,

BACKGROUND OF THE INVENTION

Lactic acid bacteria are Gram-positive bacteria that produce lactic acid by the fermentation of glucose. *Streptococcus thermophilus* is also included in this definition by convention.

Page 2, paragraph beginning at line 7,

SUMMARY OF THE INVENTION

It has now been found surprisingly that the activity of H_2O_2-producing lactic acid bacteria is considerably potentiated by the addition of one or more strains of lactic acid bacteria that are capable of utilizing arginine. Arginine forms part of various small peptides found in biological fluids and it also occurs as free arginine. Many bacterial species utilize it for their own nutrition and growth. Arginine-utilizing lactic acid bacteria can therefore deprive other, pathogenic or potentially pathogenic bacteria of a certain quantity of arginine, which - though not enough to terminate their growth - makes them more susceptible to the action of the H_2O_2 produced by the lactic acid bacteria.

DETAILED DESCRIPTION OF THE INVENTION

IN THE CLAIMS

2. (Amended) Combination according to claim 1, in which the strain of lactic acid bacteria in component (b) is [the] biologically pure *Lactobacillus brevis* [CD2 strain deposited in the DSM - Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH, Braunschweig, Germany, on February 6, 1998 with access number] DSM 11988 [under the Budapest Treaty], or mutants or derivatives thereof.

3. (Amended) Combination according to [Claims] claim 1, in which the ratio of the number of bacteria is component (a) to the number of bacteria in component (b) is from [1:00] 1:100 to 100 : 1.

6. (Amended) Combination according to claim 1 [in unit dosage units] comprising from 1 x 10^2 to 5 x 10^{11} bacteria of component (a) and from 1 x 10^2 to 5 x 10^{11} bacteria of component (b).

15. (Amended) The [composition] combination according to claim 1, wherein component (a) is *Lactobacillus crispatus* and component (b) is *Lactobacillus brevis.*

16. (Amended) The [composition] combination according to claim 1, wherein component (a) is *Lactobacillus salivarius* and component (b) is *Lactobacillus brevis.*

18. (Amended) The [composition] combination according to claim 15, wherein the ratio of the number of bacteria in component (a) to the number of bacteria in component (b) is 1:1.